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ARTICLE

PK/PD modeling to characterize placebo and treatment effect of omalizumab for chronic spontaneous urticaria

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Abstract

The pharmacokinetic (PK) characteristics of omalizumab and its pharmacodynamic (PD) effect in patients has yet to be fully characterized in chronic spontaneous urticaria, which could elucidate its pathogenesis and treatment response. This study has two objectives; (1) characterize the population PK of omalizumab and its PD effect on IgE, and (2) develop a drug effect model of omalizumab in urticaria (via change in weekly itch severity score). The target-mediated population of PK/PD model incorporating omalizumab-IgE binding and turnover adequately described PK and PD of omalizumab. The effect compartment model and linear drug effect and additive placebo response adequately described placebo and treatment effects of omalizumab. Several baseline covariates were identified for PK/PD and drug effect models. The developed model has the potential to aid in understanding variability in PK/PD as well as response to omalizumab treatment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The pharmacokinetic (PK) characteristics of omalizumab and its pharmacodynamic (PD) effect on IgE in patients with allergic asthma have been described by a target-mediated population PK/PD (PopPK/PD) model incorporating the binding of omalizumab to free IgE. However, PK/PD of omalizumab for patients with chronic spontaneous urticaria (CSU) has not been fully characterized. In addition, there is little research on pharmacometric modeling-based approaches to describe the effect of omalizumab on the symptomatic presentation of CSU, including urticaria.

WHAT QUESTION DID THIS STUDY ADDRESS?

The target-mediated PopPK/PD model incorporating omalizumab-IgE binding and turnover adequately described PKs and PDs of omalizumab.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The drug effect model adequately described placebo and treatment effects of omalizumab on improvement of weekly itch severity score in patients with CSU.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The developed drug effect model can be used for the purpose of virtual control generation or benchmarking to aid in the development of novel therapies for CSU.

INTRODUCTION

Chronic spontaneous urticaria (CSU), also referred to as chronic idiopathic urticaria (CIU), is a mast-cell driven disease that presents as recurrent urticaria and/or angioedema for at least 6 weeks. The pathogenesis of CSU is not fully established, as there is no apparent external trigger, but it is generally hypothesized to have an autoimmune origin.[1,2] Currently, second-generation H1-antihistamines are considered to be first-line treatment for patients with CSU and doses up to four times the approved dose can be prescribed if patients continue to be symptomatic.[3] Although not approved for this indication and not recommended for long-term use due to their many side effects, other add-on therapies for symptomatic patients with CSU include leukotriene receptor antagonists (LTRAs), cyclosporin A, and oral corticosteroids.[2]

Omalizumab is a humanized monoclonal antibody that binds to free immunoglobulin E (IgE), which prevents IgE from binding to its high-affinity receptor (FcεR1) on the surface of FcεR1 presenting cells, which include mast cells, monocytes, dendritic cells, basophils, and airway smooth cells.[4] Omalizumab has been approved for the treatment of CSU in adults and adolescents 12 years of age and older, and is shown to improve symptoms with an acceptable safety profile. Omalizumab has also been approved for moderate to severe persistent allergic asthma in adults and children ages 6 years and older, and for nasal polyps in adults 18 years and older.[5]

The pharmacokinetic (PK) characteristics of omalizumab and its pharmacodynamic (PD) effect on IgE in patients with allergic asthma have been described by a target-mediated population PK/PD (PopPK/PD) model incorporating the binding of omalizumab to free IgE.[6–8] Omalizumab exhibits slow absorption after subcutaneous administration, with peak serum concentrations occurring after 7–8 days. Once absorbed, omalizumab binds IgE to form "small, biologically inert, noncomplement-fixing complexes,"[7] which are then cleared through the reticuloendothelial system. Clearance is slow (around 2–3 mL/kg/day), with a terminal half-life of 26 days,[7] However, there is little data regarding omalizumab for patients with CSU. In addition, there is little research on pharmacometric modeling-based approaches to describe the effect of omalizumab on the symptomatic presentation of CSU, including urticaria. This study has two objectives; (1) characterize the PopPK of omalizumab and its PD effect on IgE, and (2) develop a longitudinal disease model of CSU that describes the drug effect of omalizumab on a patient's disease severity (via change in weekly itch severity score).[9]

METHODS

Clinical studies used in the analysis

The PopPK/PD development model for omalizumab/placebo-treated patients included data from MYSTIQUE (NCT00866788),[10] ASTERIA I (NCT01287117),[5] ASTERIA II (NCT01292473),[11] and GLACIAL (NCT01264939).[12] Patients were randomized to receive either omalizumab or placebo as a single dose or every 4 weeks subcutaneously for 7 to 24 weeks. All four studies were used to develop the PopPK/PD model, whereas only the phase III studies (ASTERIA I, ASTERIA II, and GLACIAL) were used to develop the drug response model, given MYSTIQUE was a single dose study and did not have the dosing data required to develop a longitudinal dose response model. A summary of the studies is provided in Table S1. All inclusion/exclusion criteria were upheld.

MYSTIQUE ($N = 90$) was the only phase II study. It evaluated the efficacy of omalizumab compared with placebo in patients with refractory CSU receiving concomitant H1 antihistamine therapy, with a primary end point of change from baseline in weekly itch severity score at week 4. The weekly itch severity score is the sum of a patient's self-reported daily itch severity scores (ranging from 0 to 21) over 7 days. The daily itch severity score is the average of the morning and evening scores on a scale of 0 (none) to 3 (severe). ASTERIA I ($N = 306$) and ASTERIA II ($N = 308$) evaluated the efficacy and safety of omalizumab versus placebo in patients with CIU/CSU who were symptomatic despite treatment with approved doses of H1 antihistamines, and had the primary end point of change from baseline in weekly itch severity score at week 12. The objective of GLACIAL ($N = 326$) was to evaluate the safety of omalizumab in patients receiving add-on therapies for CIU/CSU through the primary end point of percentage of participants with adverse events, with efficacy defined as change from baseline in weekly itch severity score at week 12 as a secondary end point. All study protocols were approved by institutional review boards and/or independent ethics committees at each site and written informed consent was

obtained from each participant or a parent/legal guardian if the participant was less than 18 years of age.[5,10–12]

Assays

Serum samples were analyzed for total omalizumab (fluorometric enzyme-linked immunosorbent assay [ELISA]), free IgE (ImmunoCAP fluoroenzyme immunoassay), and total IgE levels (ELISA). Baseline, on-treatment, and follow-up PK and IgE data were analyzed. For the omalizumab assay, the lower limit of quantification (LLOQ) was 28 ng/mL, with no upper limit of quantification (ULOQ). Free omalizumab assay was not developed due to technical challenges. The LLOQ and ULOQ for free IgE were 0.83 IU/mL and 62.0 IU/mL, respectively. The LLOQ and ULOQ for total IgE were 2 IU/mL and 5000 IU/mL, respectively. Baseline IgE levels were measured using the total IgE assay because it has a larger dynamic range than the free IgE assay. The baseline IgE levels are expected to be the same for total IgE and free IgE in the absence of omalizumab.

Software

Omalizumab PopPK/PD modeling was performed with NONMEM 7.1.2 and the First-Order (FO) method was utilized for estimation steps as consistent with historical PopPK/PD models.[7] Drug effect modeling was performed with NONMEM 7.4.3 with First-Order Conditional Estimation as the estimation method.[13] For both models, Pearl-Speaks-NONMEM (PsN; Uppsala University, Uppsala, Sweden) was used to perform simulations and evaluate/validate the model using predictive checks.[14–16] Simulations and plotting of simulations utilized R Studio software in addition to Comprehensive R Archive Network (CRAN) packages.[17]

Data handling and missing values

Patients were included in the PopPK/PD analysis dataset if they had at least one dose of study drug and provided at least one PK sample (PK-evaluable population). PK observations were excluded from the analysis if missing, below the lower quantification limit (BLOQ), or above the ULOQ concentration values. Most omalizumab and total IgE samples were quantifiable. Patients were included in the drug effect analysis if they provided at least one evaluation of itch severity score after baseline. Baseline IgE was an important PK/PD covariate that directly impacted the fitting of the post-treatment total and free IgE data and its impact on model parameters was sensitive to BLOQ imputation. Therefore, patients with BLOQ or ULOQ baseline IgE values were excluded from analysis. Baseline IgE values that were above the ULOQ were set to 5000 IU/mL (<1% of samples) and were included in the analysis. A full summary of the analytes can be found in Table S2.

Missing covariate values for body mass index (BMI), body weight, and age values were imputed as 30 kg/m^2, 80 kg, or 40 years, respectively, as these were typical values representative of the CSU population. Missing histamine-2 receptor antagonists (H2RAs), LTRA, or anti-FcεR1 autoantibody status (presence of IgG autoantibodies against the high affinity IgE receptor, FcεR1), were imputed as absent or negative. Data points were deemed outliers if the absolute value of the weighted residual was greater than 5 and were excluded from the dataset.

Population PK/PD model

Model structure

The model adopted the same model structure as the omalizumab PopPK/PD model for patients with allergic asthma incorporating omalizumab-IgE binding and turnover with FO absorption and FO elimination.[6–8] A visual diagram of the model can be found in Figure S1, and the NONMEM model code is described in Text S1. The model is comprised of three differential equations describing the disposition of free omalizumab, total omalizumab (free + complex), and total IgE (free + complex). The differential equations with model parameters are as follows:

$$\frac{dA}{dT} = -k_a \cdot A$$

$$\frac{dX_T}{dT} = k_a \cdot A - \frac{CL_X}{V_X} \cdot X - \frac{CL_C}{V_C} \cdot C$$

$$\frac{dE_T}{dT} = R_E - \frac{CL_E}{V_E} \cdot E - \frac{CL_C}{V_C} \cdot C$$

where A is the amount of omalizumab in the absorption compartment, X_T is total omalizumab, E_T is total IgE, C is the amount of omalizumab-IgE complex, E is the amount of free IgE, and X is the amount of free omalizumab. The amount of complex C can be solved from the equations:

$$C = \frac{\left(\frac{K_D V_X V_E}{V_C} + X_T + E_T\right) - \sqrt{\left(\frac{K_D V_X V_E}{V_C} + X_T + E_T\right)^2 - 4 X_T E_T}}{2}$$

and

$$X = X_T - C$$

$$E = E_T - C$$

$$K_D = K_{D0} - \frac{{X_T}^{\alpha}}{E_T}$$

The model parameters are defined as follows: k_a is the absorption rate constant, CL_X and V_X are the apparent clearance and volume of distribution of free omalizumab, CL_C and V_C are the apparent clearance and volume of distribution of complex, CL_E and V_E are the apparent clearance and volume of distribution of free IgE (model assumes $V_X = V_E$ which is consistent with the model for allergic asthma patients), R_E is the rate of synthesis of free IgE, K_D is the apparent in vivo equilibrium binding constant, K_{D0} is the K_D when total omalizumab and total IgE have equal molar concentration, and α is a coefficient that characterizes the change in the apparent binding constant according to the ratio between total omalizumab and total IgE.

Base model development

The parameters and covariates from the patients with allergic asthma were used as a starting point for model development. The model was fine-tuned in a two-step process: (1) volume of distribution of complex V_C and its interindividual variability was estimated with intensively sampled phase II data, and (2) all parameters then estimated except for V_C with the entire dataset. This fine-tuning is due to difficulty in accurately estimating V_C in predominantly sparsely sampled phase III datasets. Furthermore, covariates whose 95% confidence intervals had no overlap were excluded. This simplified model was considered as the base model for the testing of CSU-specific covariates.

Population PK/PD covariates

Additional CSU-specific covariates for the PopPK/PD model were selected with forward-addition ($p < 0.05$) and backward-elimination ($p < 0.001$) process. Additional candidate covariates specific to patients with CSU included the presence/absence of the anti-FcεR1 autoantibodies as measured by a functional test, the presence/absence of concomitant H2RAs or LTRAs, and an effect of the GLACIAL study which consisted of a different patient population with additional concomitant medications (LTRAs). Finally, sensitivity of total omalizumab trough concentrations to covariates was analyzed using a tornado plot by varying covariates to extreme values (at 5th and 95th percentiles of the population) and comparing the model predictions with the overall distribution of trough concentrations in the CSU population.

Drug effect model

Model structure and development

The developed PopPK/PD model was used to simulate individual PK profiles with empirical Bayes estimates and total omalizumab concentration was used as an input to the drug effect model with change in weekly itch severity score as the end point. Various models, including the direct effect and effect compartment model, were tested and compared based on objective function values, goodness-of-fit plots, precision, and visual predictive checks (VPCs). The effect compartment model was preferred over the direct effect model due to the delayed reduction of itch severity score compared to PK accumulation. An additive placebo effect was provided to describe the decrease to steady-state plateau seen in placebo patients. The empirical equation for the outcome captures the mechanism of an effect compartment model in which the drug effect is driven by the concentration (which is delayed relative to the plasma concentration by a first-order rate constant, K_{E0}), and the placebo effect as follows:

$$\text{Weekly itch severity score} = \text{Base}_{\text{itch}} - \text{Slope} \cdot C_{\text{bio}} - E_{\text{placebo}} \cdot \left(1 - 10^{-K_{\text{placebo}} \cdot \text{time}}\right)$$

Where $\text{Base}_{\text{itch}}$ is baseline itch severity score, Slope is the slope term in a linear drug effect model, C_{bio} is the biodistribution (effect) compartment concentration of total omalizumab, K_{placebo} is the rate of onset of placebo effect, and E_{placebo} is the placebo effect on itch severity score at plateau. Total omalizumab concentration in the effect compartment was an ordinary differential equation shown as follows:

$$\frac{dC_{\text{bio}}}{dt} = K_{E0} \cdot \left(\frac{X}{V_X} + \frac{C}{V_C}\right) - K_{E0} \cdot C_{\text{bio}}$$

With $X/V_X + C/V_C$ corresponding to total omalizumab concentration in the central compartment, and K_{E0} as the effect-site elimination rate constant. The full NONMEM model code is described in Text S2. A linear drug effect was chosen over an E_{max} model, as the latter caused over-parameterization and high relative standard error percentages. Due to the difficulty of estimating placebo and drug effect parameters simultaneously, a stepwise method was used to estimate placebo parameter values. The bounded nature of the end point was not explicitly accounted for in the model, and potential bias of this approach was examined by comparing the number of predictions less than zero against the number of observed events at zero.

Covariate selection and estimation methods

Effects of covariates were tested on all model parameters ($K_{placebo}$, $E_{placebo}$, K_{E0}, and Slope). Similar to base model development, effects of covariates on placebo response were first estimated, then fixed when estimating covariate effects on drug effect parameters. Baseline demographic and study-related covariates included were age, body weight, sex, race, ethnicity, baseline itch severity score, and relevant concomitant medications (H2RAs and LTRAs). Baseline IgE levels were log-transformed given the wide dynamic range of values. Categorical covariates (race, ethnicity, and relevant concomitant medications) were grouped based on the highest frequency observations. Race was categorized as "White," "Black," and "other," and defined by three dummy variables for each category. Ethnicity was categorized as "Hispanic/Latino origin" or "non-Hispanic/Latino origin." Two covariates accounted for specific concomitant medications to examine their influence on patient response to drug effect based on the definitions in the original studies. One covariate accounted for H2RAs as a concomitant medication and the second covariate defined LTRAs as a concomitant medication. Covariate selection was performed using forward-addition, backward-elimination ($p < 0.05$ for both) stepwise covariate modeling (scm). To visualize the magnitude of the covariate effects, predictive simulations were performed with the final model at the 5th, 50th, and 95th percentile values for continuous covariates or each categorical covariate value.

RESULTS

Table 1 summarizes the data included in the PopPK and drug effect analysis. The PopPK model building and validation used data from 756 out of 1030 patients across MYSTIQUE, ASTERIA I, ASTERIA II, and GLACIAL. Placebo patients and patients marked for exclusion in the data set (see Data Handling) or those with BLOQ baseline IgE values were excluded.

The drug effect model building and validation used data from 921 out of 975 patients across ASTERIA I, ASTERIA

TABLE 1 Descriptive statistics of the main covariates at baseline in the PK/PD population.

Variable	MYSTIQUE ($n = 90$)	ASTERIA I ($n = 306$)	ASTERIA II ($n = 308$)	GLACIAL ($n = 326$)	Total ($n = 1030$)
Continuous covariate, median [min, max]					
Age, years	40 [15, 70]	41 [12, 74]	42.5 [14, 75]	44.5 [14, 75]	42 [12, 75]
Baseline weight, kg	75 [46, 148]	79.97 [34.8, 138]	79.5 [43, 188]	79.05 [45.9, 172]	79 [34.8, 188]
Baseline BMI, kg/m^2	27.3 [14.9, 56.3]	28.25 [15.76, 53.97]	28.29 [17.92, 55.89]	27.92 [18.18, 69.32]	28.01 [14.9, 69.32]
Baseline IgE (IU/mL)[a]	86 [2, 1500]	83 [2, 5000]	78 [2, 1450]	78 [2, 3050]	79.5 [2, 5000]
Baseline itch severity score	NA[b]	14 [8, 21]	13.5 [8, 21]	13.75 [7.5, 21]	13.5 [7.5, 21]
Categorical covariate, *N*					
Sex					
Male	29	85	76	91	281
Female	61	221	232	235	749
Race					
White	75	254	262	290	881
African American or Black	8	33	25	21	87
Other or unknown	7	19	21	15	62
Ethnicity					
Hispanic or Latino	4	20	25	23	72
Not Hispanic or Latino or unknown	86	286	283	303	958
Concomitant medications					
H2 antihistamines	6	36	28	282	352
Leukotriene receptor antagonists	1	16	21	151	189

Abbreviations: BMI, body mass index; NA, not applicable; PK/PD, pharmacokinetic/pharmacodynamic.

[a]The lowest value of baseline IgE = 1 was removed.

[b]MYSTIQUE was not included in the drug effect model endpoint analysis as it was a single dose study.

II, and GLACIAL. It should be noted that a much higher ratio of patients enrolled in GLACIAL were taking H2RAs or LTRAs, but no other obvious differences were observed among the three studies.

Population PK/PD model

Analyte summary

The dataset consisted of 773 subjects, of which ~54% received 300 mg and 20% received 75 or 150 mg of omalizumab. Only 21 (~3%) subjects received 600 mg, all as a single dose in MYSTIQUE. In total, 17 patients had baseline IgE values that were BLOQ. Most omalizumab, total IgE, and free IgE samples were quantifiable, and samples with BLOQ or ULOQ concentration values for omalizumab, total or free IgE were excluded from the analysis. The full summary table included in the analysis, excluding the placebo patients and samples marked for exclusion in the dataset, can be found in Table S2.

Model parameter estimates

The statistically significant parameter-covariate relationships in the final model are as follows:

$$\mathrm{CL}_x = 0.259 \times (\mathrm{BWT} \div 80)^{0.605} \times (\mathrm{BMI}/30)^{0.587} \times e^{(-0.0672 \times X_{\mathrm{FC}})} \times e^{(-0.0700 \times X_{\mathrm{H2}})}$$

$$\mathrm{CL}_E = 1.68 \times (\mathrm{BWT} \div 80)^{0.605} \times (\mathrm{BIGE}/80)^{-0.158}$$

$$\mathrm{CL}_C = 0.444 \times (\mathrm{BWT} \div 80)^{0.605}$$

$$V_x = V_E = 8.92 \times (\mathrm{BWT} \div 80)^{0.756}$$

$$V_C = 5.79 \times (\mathrm{BWT} \div 80)^{0.756}$$

$$R_E = 289 \times (\mathrm{BWT} \div 80)^{0.514} \times (\mathrm{BIGE}/80)^{0.838}$$

$$K_{D0} = 2.12 \times (\mathrm{BIGE}/80)^{-0.0780}$$

Where X_{FC} is the presence of anti-FcεR1 autoantibodies, X_{H2} is the use of H2RAs. BIGE is baseline IgE and BWT is body weight. The parameter estimates are shown in Table 2. The PK/PD parameters were estimated with generally good precision, with percent SEs less than or equal to 10% for most structural parameters, including clearance and volume estimates, binding constant, and IgE synthesis rate. Overall, the key PK/PD parameter values were similar between patients with CSU and patients with allergic asthma.[6–8]

Model diagnostics

Figure 1 shows the VPCs, which suggests a generally accurate fit between the model prediction and data. In general, the total omalizumab concentrations were well fit by the predictions. Total IgE had a slight underprediction in the first 4 weeks in MYSTIQUE, which may be attributed to the large variability during this period in the single-dose study. Free IgE appeared to have a slight overprediction at 40 weeks, which can be attributed to the large percentage of ULOQs in the washout period in the phase III studies. In addition, the plots of measured versus predicted free IgE concentrations showed characteristic tails at the extremes of the predicted values (i.e., the range of predictions was greater than the range of measured concentrations), which occurs when measured values are censored both below the LLOQ and above the ULOQ. Overall, the residual diagnostics suggest minimal deviation between observed and predicted values for omalizumab across all timepoints in all studies, and most of the time points (e.g., weeks 12 and 24) for free and total IgE (Figure S2). The Monte-Carlo simulated residual diagnostics closely matched the traditional linear approximation diagnostics (Figure S3). The similarity suggests that the linear approximation used in the FO method is nearly equivalent to the more theoretically correct Monte-Carlo simulation approach. Across all studies, the 90% prediction intervals (shaded region) generally covered the spread of data and the predicted median. The 5th and 95th percentiles (solid black lines) were similar to the measured percentiles (dashed lines) for all three analytes. Overall, the model described omalizumab PKs and PDs adequately across all studies.

Covariate analysis results

Figure 2 shows the impact of statistically significant covariates, varied one at a time, on week 12 trough levels of total omalizumab in the MYSTIQUE/ASTERIA I/ASTERIA II populations at the dose of 300 mg omalizumab every 4 weeks. The corresponding results are also tabulated in Table 2. BMI and weight contributed most to the variability in week 12 trough levels. Other covariates (anti-FcεR1 autoantibodies, H2RAs, and baseline IgE) had negligible overall impact on omalizumab trough levels. The variability in trough concentrations with extreme values of body mass index ranged from −24% to +26% relative to the reference patient and ranged from −22% to +25% for body weight. No single covariate contributed more than a 26% change in trough value, which was small compared with the −52% to +104% range (5th to 95th percentile) in the

TABLE 2 PopPK/PD parameter estimates.

Model parameter, (Variable, units)	Estimate	SE (%)	95% CI	IIV (%CV)	Shrinkage (%)
Structural parameters					
Apparent clearance omalizumab, L/day	0.26	2	[0.247, 0.271]	35	48
Apparent clearance IgE, L/day	1.68	8	[1.41, 1.95]	6	94
Apparent clearance omalizumab-IgE complex, L/day	0.44	9	[0.36, 0.53]	49	36
Apparent volume omalizumab and IgE, L	8.92	2	[8.59, 9.25]	29	62
Apparent volume complex, L[a]	5.79	FIX		47	69
Absorption rate, 1/day	0.92	9	[0.75, 1.09]	122	72
Lag time, day	0.060	3	[0.056, 0.064]		
Apparent binding constant, nM[b]	2.12	9	[1.73, 2.51]	31	67
Alpha, α[b]	0.12	20	[0.07, 0.17]		
IgE production rate, ×g/day	289	8	[243, 335]		
Covariates					
Body weight on CL_X, CL_E, CL_C	0.61	20	[0.37, 0.84]		
Body mass index on CL_X	0.59	21	[0.35, 0.82]		
Anti-FcεRI autoantibodies (Yes vs. No) on CL_X	−0.067	48	[−0.13, −0.0041]		
H2RAs on CL_X (Yes vs. No)	−0.070	39	[−0.12, −0.017]		
Baseline IgE on CL_E	−0.16	13	[−0.20, −0.11]		
Bodyweight on V_X, V_E, V_C	0.76	9	[0.62, 0.89]		
Bodyweight on R_E	0.51	23	[0.28, 0.75]		
Baseline IgE on R_E	0.84	2	[0.80, 0.88]		
Baseline IgE on K_{D0}	−0.078	32	[−0.13, −0.029]		
Covariances and IIV					
Covariance CL_X and V_X	0.080				
IIV omalizumab (%)[c]	24	10			
IIV total IgE (%)[c]	25	6			
IIV free IgE (%)[c]	43	9			

Abbreviations: CI, confidence interval; CV, coefficient of variation; IIV, interindividual variability reported as the square root of the variance of log-normal random effects; PopPK/PD, population pharmacokinetic/pharmacodynamic; SE, standard error, as a percentage of the estimate.

[a]Parameter value and variability fixed from phase II estimation.

[b]K_D: $K_{D0}\,(X_T/E_T)^{\alpha}$, where X_T is total omalizumab and E_T is total IgE.

[c]For IIV parameters, the estimate is the square root of the variance, and SE (%) is the standard error of the variance of log-normal random effects divided by the estimated variance.

trough concentration across the population relative to the reference patient. The numerical results can be found in Table S3.

Drug effect model

The covariates retained in the final baseline model were baseline itch severity score on the placebo effect at plateau (E_{placebo}), baseline IgE, log transformed baseline IgE (Log_{10}(Baseline IgE)) and ethnicity on the effect-site elimination rate constant (K_{E0}), and baseline itch severity score, body weight, and baseline IgE on the slope term (Slope). The statistically significant parameter-covariate relationships in the final model are as follows:

$$E_{\text{placebo}} = 6.73 \times (1 + 0.254 \times (\text{Baseline itch severity score} - 14))$$

$$K_{E0} = 0.0937 \times (\text{Ethnicity} \times (1 + 0.568)) \times (1 + 0.141 \times (\text{Log}_{10}(\text{Baseline IgE}) - 4.39))$$

$$\text{Slope} = 0.0172 \times (1 + 0.0787 \times (\text{Baseline itch severity score} - 14)) \times (1 + 0.0143 \times (\text{Body weight} - 79.5)) \times (1 + 0.236 \times (\text{Log}_{10}(\text{Baseline IgE}) - 4.39))$$

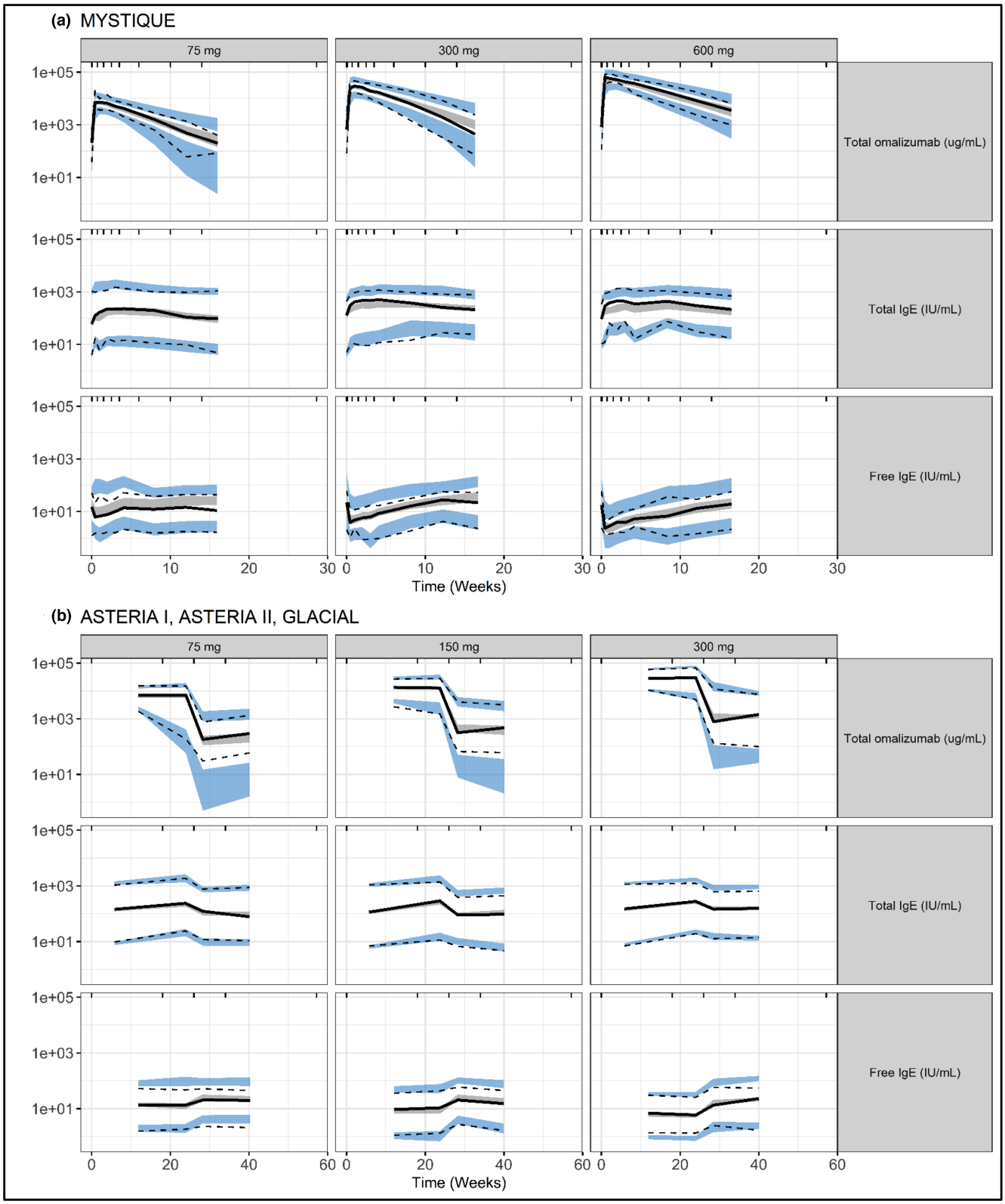

FIGURE 1 Visual predictive checks for MYSTIQUE (q4577g) and ASTERIA I (q4881g), ASTERIA II (q4882), and GLACIAL (q4883). The dark black line shows the observed data at median values, wheREAS the dotted black lines represent the 5th and 95th percentile observed values. The blue shaded areas are the 95% prediction intervals for the 5th, 50th, and 95th range of predictions.

Of note, ethnicity was defined as a binary variable if the patient identified/did not identify as of Hispanic/Latino origin. The model after the scm step included a H2RA-related covariate effect, but it resulted in the skew of VPC for GLACIAL, potentially due to a significant imbalance in the proportion of subjects taking H2RAs

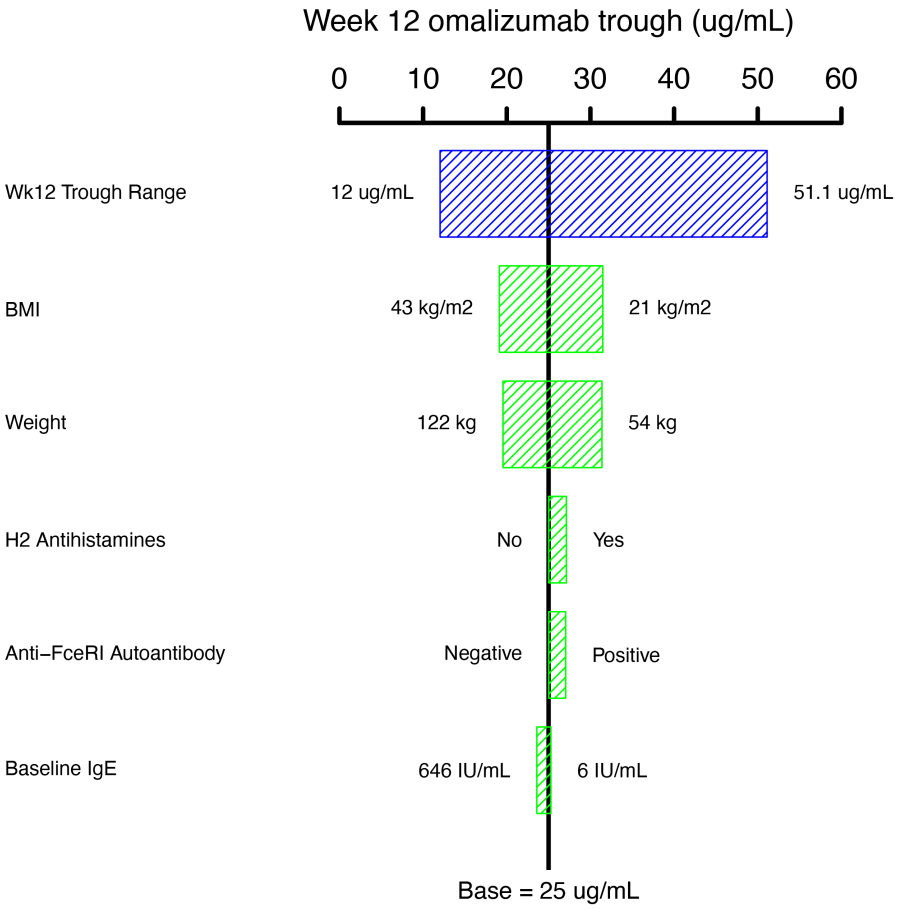

FIGURE 2 Covariate sensitivity of total omalizumab trough levels at week 12 in patients with CSU receiving omalizumab 300 mg every 4 weeks (q4w). The vertical line represents the predicted week 12 trough total omalizumab level of 25.0 μg/mL in a typical patient with CSU receiving a 300 mg q4w regimen. This typical patient has weight of 80 kg, BMI of 30 kg/m^2, baseline IgE of 80 IU/mL, is not receiving H2RAs, and negative for the anti-FCεRI autoantibody. The top blue hatched bar shows the 5th to 95th percentile range of modeled week 12 trough levels across the patient population. The hatched green bars show, in ranked order of importance, the variation in modeled trough levels as covariates are changed one at a time to extreme values. For continuous variables, the extreme values are 5th and 95th percentiles of the population. BMI, body mass index; CSU, chronic spontaneous urticaria.

in GLACIAL compared to ASTERIA I and II. Therefore, the effect of the H2RA-related covariate was excluded from the final model. As such, incorporating the model with placebo covariates improved the delta OFV by −6.14 points, and the incorporation of both placebo and drug effect covariates resulted in a delta OFV of −119.63 points.

The parameter estimates for the final model parameters are provided in Table 3. Overall, the model provided reasonable estimates with relative standard error of <10% for most parameters. The VPCs for each study included in the drug effect model are shown in Figure 3a and show that the observed data at 5th–50th–95th percentile values for each study largely fit within the predicted 95% confidence interval simulations of the model. The placebo effect and drug effect incorporated into the model also show the placebo effect reaching plateau after several weeks, and a linear drug effect with a delay in the onset of drug effect and return to baseline. The goodness-of-fit plots for each study and VPCs for the base structural model are shown in Figures S4 and S5. Of note, the predictions were bounded at zero for generating VPCs given the non-negative nature of the end point. No bias was found from bounding end point predictions when comparing the number of predictions equal to/below zero against the number of observed events, which is shown in Figure 3b.

When examining the magnitude of the covariate effects (Figure 4), patients with higher baseline itch severity scores displayed higher drug and placebo effects. Patients with higher body weight and higher baseline IgE levels displayed increased response to the drug effect. Patients of Hispanic/Latino ethnicity showed a slight change in drug effect.

DISCUSSION

Overall, the PK and PD characteristics of omalizumab in CSU were adequately described by a target-mediated PopPK/PD model incorporating omalizumab-IgE binding and turnover, with the same structure and similar parameter estimates as those for allergic asthma. This suggests that the omalizumab-IgE pharmacology is similar between patients with allergic asthma and patients with CSU. Standard residual diagnostics, VPCs, as well as newer diagnostics using Monte-Carlo simulations all supported the adequacy of the model. Body weight, baseline IgE, BMI, anti-FCεRI autoantibodies and concomitant use H2Ras were identified as statistically significant covariates on PopPK/PD parameters.

TABLE 3 Parameter estimates for the final model.

Parameter	Estimate	RSE (%)	95% CI	IIV (CV%)	Shrinkage
Placebo model only					
Baseline itch severity score ($Base_{itch}$)	13.5	2	[13.01, 14.01]	15	15
Rate of onset of placebo effect ($k_{placebo}$, 1/d)	0.033	16	[0.024, 0.042]	11	27
Placebo effect on itch severity score at plateau ($E_{placebo}$)	6.73	8	[5.86, 7.61]	21	10
Baseline itch severity score on $E_{placebo}$	0.0254	58	[0.001, 0.050]		
Add. error	2.62	3	[2.47, 2.76]		
Drug effect model					
Effect-site elimination rate constant (K_{E0}, 1/d)	0.0937	5	[0.086, 0.10]	15	54
Slope term in linear drug effect model (slope)	0.0172	7	[0.015, 0.21]	9	32
Ethnicity on K_{E0}	0.568	47	[0.080, 1.06]		
Log_{10}(Baseline IgE (IU/mL)) on K_{E0}	0.141	31	[0.073, 0.21]		
Baseline itch severity score on slope	0.0787	20	[0.053, 0.10]		
Body weight (kg) on slope	0.0143	23	[0.009, 0.020]		
Log_{10}(Baseline IgE (IU/mL)) on slope	0.236	8	[0.20, 0.27]		

Abbreviations: CI, confidence interval; CV, coefficient of variation; IIV, interindividual variability reported as the square root of the variance of log-normal random effects; RSE, relative standard error.

Data from ASTERIA I, ASTERIA II, and GLACIAL were used to develop and validate a drug effect model that described the change in weekly itch severity score after omalizumab administration and dose response through an effect compartment structural base model with linear drug and additive placebo effects. The incorporation of an effect compartment and linear drug effect described the time delay in drug effect and decrease from the baseline itch severity score seen in all three studies. It also captured the return to baseline itch severity score once dosing stopped. The additive placebo effect captured the decrease from baseline itch severity score to a plateaued steady-state value. The empirical equation that was derived to predict the change in weekly itch severity score successfully characterized the drug response trajectories. Despite the model predicting below zero, the proportion of observations predicted to be at or below zero corresponded with the trajectory of observed values equal to zero.

Covariate analysis using stepwise covariate modeling showed body weight, ethnicity, baseline total IgE, and baseline itch severity score to be significant covariates of the drug effect model. Higher baseline itch severity score was associated with an increased response, as expected. This is in line with subgroup analyses that were performed in ASTERIA I, II, and GLACIAL that found patients with higher baseline itch severity score had larger absolute reductions compared with patients with lower baseline weekly itch severity score. This was also similar for the observed treatment effect.[5] Although ethnicity was a statistically significant covariate, the majority of subjects were classified as ethnically "Not Hispanic or Latino" (92.8%). The lack of ethnic diversity limits the conclusions that can be made regarding the effect of ethnicity on drug and placebo effect.[5] Lower body weight was associated with slightly less response; however, lower body weight should result in higher exposure and thus higher response which was already captured by the PK/PD model. As such, the difference in exposure is unlikely to be the reason for this association and there may be an imbalance in unobserved variables across different body weights. Higher baseline IgE was associated with an increased response, though higher baseline IgE is expected to result in lower receptor occupancy as well as higher free IgE after omalizumab administration. Although the biological mechanism is unclear, one possible interpretation is that higher baseline IgE may be an indicator of IgE involvement in the pathogenesis of CSU.

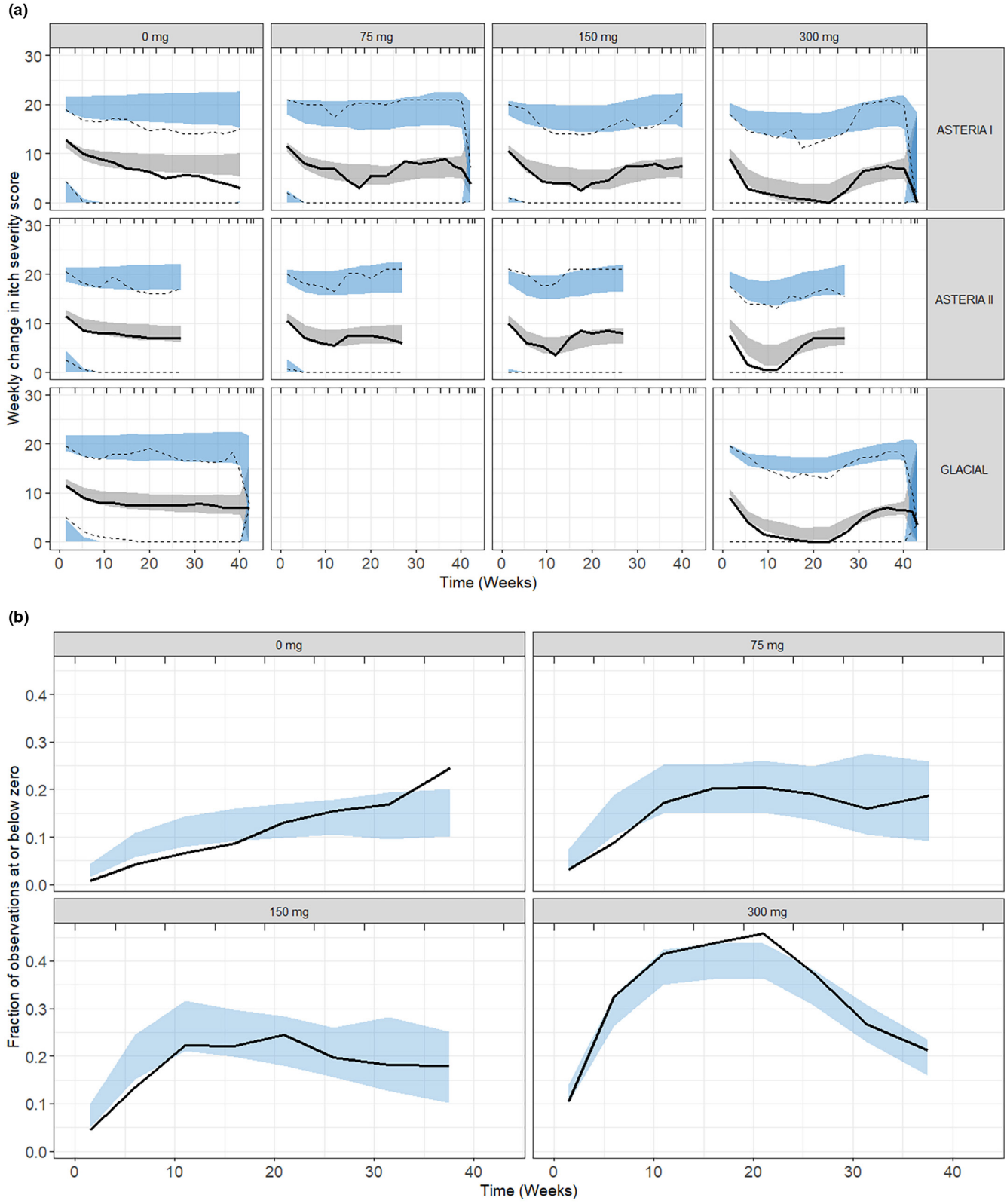

FIGURE 3 (a) Visual predictive checks of the drug effect final model for ASTERIA I, II, and GLACIAL. The dark black line shows the observed data at median values, whereas the dotted black lines represent the 5th and 95th percentile observed values. The blue shaded areas are the 95% prediction intervals for the 5th, 50th, and 95th range of predictions. (b) Percentage of predictions at or below zero versus the number of observed events (weekly itch score) at zero over time.

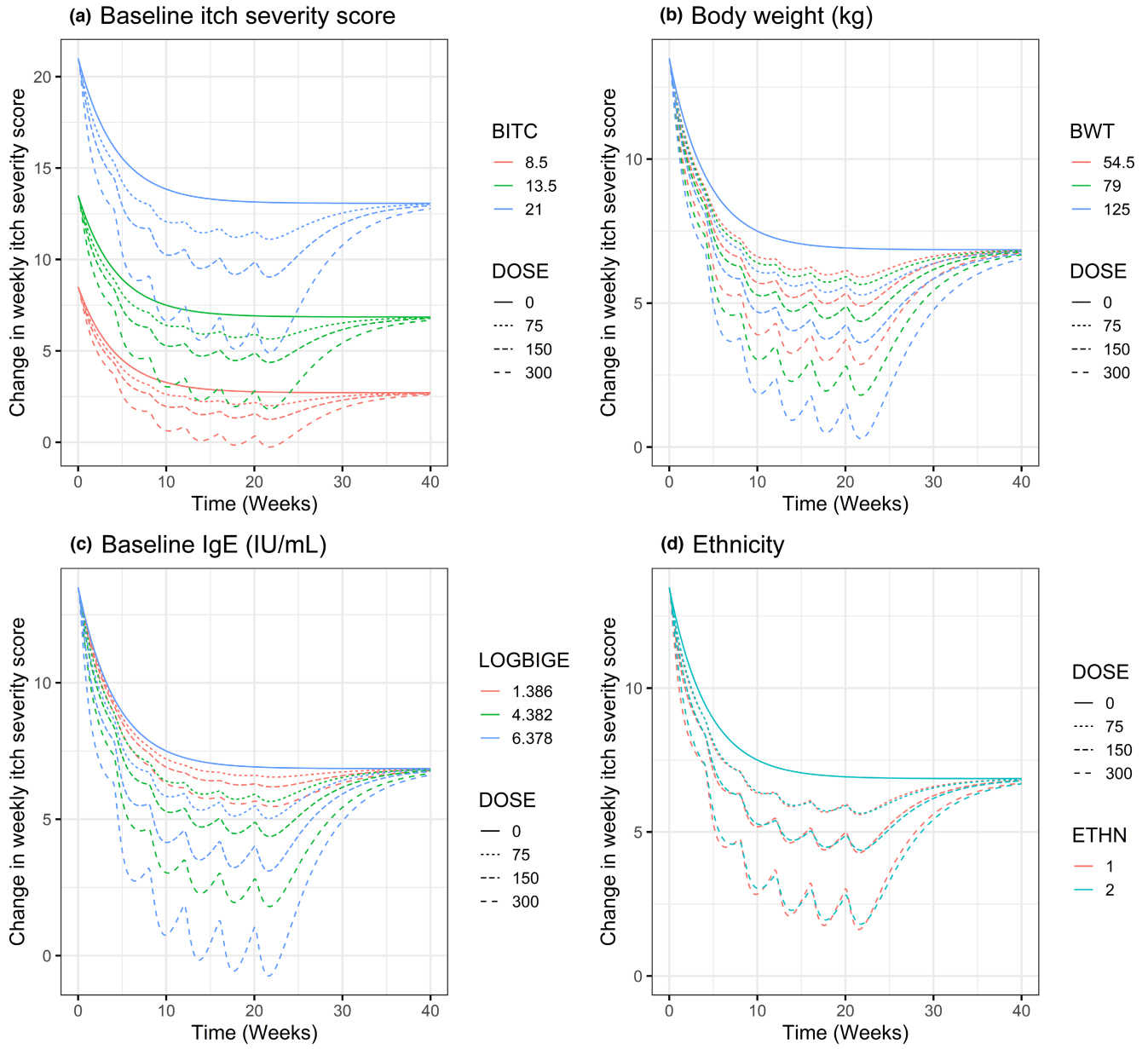

FIGURE 4 Predictive simulations visualizing covariate effects on simulated change in weekly itch severity score from baseline. BITC, baseline itch severity score; BWT, body weight; LOGBIGE, Log function of baseline IgE; ETHN, ethnicity, classified as 1: Hispanic/Latino origin. 2: Non-Hispanic/Latino origin.

The developed model can have multiple applications. One such application is for patients enrolled in clinical studies for CSU indications. This model allows for the generation of a virtual control patient to observe placebo response compared to expected trajectory—a "virtual twin" for patients who received active treatment to augment the interpretation of the treatment effect. Another application is to generate a counterfactual omalizumab-treated patient to compare with the treatment effects of other novel therapies when omalizumab is not included as a comparator arm in clinical studies. The model would be particularly useful should there be a new trial with different patient demographics compared to the previous studies. It is important to note that although the incorporation of these baseline covariates showed some improvement in the model's objective function values, further evidence is needed to translate these associations into clinical relevance. This is more relevant given the model development approach utilized a liberal criterion for covariate selection with $p < 0.05$ for backward elimination, for the purpose of maximizing the predictive power rather than defining clinically actionable insights based on patient covariates. In addition, the model is not fully mechanistic—the purpose was to describe individual patient profiles and understand potential relationships between individual profiles at a covariate effect. However,

this does not diminish the ability to generate the virtual control/twin patient to compare with observed placebo/treatment responses, particularly in future CSU trials that do not have an omalizumab-treatment arm.

AUTHOR CONTRIBUTIONS

E.O., R.W., K.L., Y.Z., J.J., V.P., K.W., R.O., and K.Y. wrote the manuscript. E.O., R.W., K.L., Y.Z., and K.Y. designed the research. E.O., R.W., K.L., Y.Z., and K.Y. performed the research. R.W., K.L., Y.Z., E.O., and K.Y. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

K.L., Y.Z., J.J., V.P., K.W., R.O., and K.Y. are current or former employees of Genentech, Inc. (a member of the Roche group) and own or owned stock in F. Hoffman-La Roche. E.O. is employed as a postdoctoral fellow with Genentech, Inc. and the University of the Pacific. R.W. is a salaried employee of Quantitative Solutions Inc., which was contracted by Genentech, Inc.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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